

## **ATTACHMENT A**

### **Remarks**

Claims 24-63 are pending in the present application. By this Amendment, Applicant has amended claims 24, 25, 43 and 44. Applicant respectfully submits that the present application is in condition for allowance based on the discussion which follows.

The Specification was object to for including an informality in that the status of the parent application no. 09/958,333 has not been updated. By this Amendment, Applicant has amended the first paragraph of the Specification to indicate that the parent application is now abandoned thereby obviating the objection to the Specification.

Claims 29, 32, 50 and 53 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. It was alleged that the claims include subject matter that was not described in the Specification in such a way to reasonably convey to one in the relevant art that the inventor at the time of the application had possessed the invention.

Contrary to this rejection, the subject matter of claims 29, 32, 50 and 53 are fully supported by at least original claims 18 and 22 which recite the preparation is washed with an aqueous solvent (claim 18) and a time period of at least seven days has lapsed between the extraction and free sugar removal (claim 22). Therefore, the Specification as filed, conveys to one of ordinary skill of the art that the inventor, at the time the application was filed, had possession of the claimed invention. Accordingly, Applicant respectfully request that the rejections to claims 29, 32, 50 and 53 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claims 1-63 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 24 and 43, were rejected for including the term “derivative” and for using of the term “comprising”, both of which have been obviated by this Amendment, in which term “derivative” has been removed and the Markush group has been amended in accordance with U.S. claim practice. Further, claims 25 and 44 were rejected for including the phrase “e.g.”, which has been removed from these claims by this Amendment. Therefore, the Applicant respectfully submits that the claims are now in compliance with 35 U.S.C. § 112, second paragraph.

Claims 24-63 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cham et al. (hereinafter Cham). The Examiner alleges that the present claims are directed to a method of preparing a glycoalkaloid preparation which includes the step of removing essentially all free sugars derived from the glycoalkaloid, compositions produced by such method and a method of treating cancer.

Contrary to the Examiner's assertion, the present invention is not obvious in view of Cham. The present invention is based on the discovery that the activity of BEC, an extract from certain plants (e.g. Devil's apple), is deleteriously affected by free sugars (rhamnose) that are a degradation product present in BEC. Prior to the present invention this problem was not known. With knowledge of this problem, the inventor found that "cleaning" a BEC preparation to remove degradation products in the form of sugars increases the activity of BEC enabling smaller effective doses of BEC to be administered than what was otherwise the case. Importantly, prior to the

present invention, the deleterious effects caused by degradation products in BEC were not known.

Contrary to the Examiner's assertion, it would not have been obvious for one of ordinary skill in the art at the time of the invention to remove free rhamnose resulting from the degradation from BEC in order to improve its activity. Absent impermissible hindsight, one of ordinary skill in the art at the time of the invention and knowledge of the state of the art and in particular, the nature of the problem addressed by the invention, would not have been motivated as alleged by the Examiner.

Furthermore, Applicant respectfully submits that prior to the present invention, the problem to the present invention solves was not known. There is no suggestion or motivation for one to believe removing the rhamnose would provide a suitable and superior product. Therefore, one of ordinary skill in the art would not be motivated to remove free rhamnose as claimed.

Moreover, Cham fails to provide any motivation for one of ordinary skill in the art to remove free rhamnose. The studies concerning rhamnose in Cham sought to learn more about the nature of the binding of the active agents in BEC to cancer cells. Cham established that the binding "may be mediated through the monosaccharide rhamnose" (see summary in Cham). This is in the context of rhamnose being a part of solasonine, solamargine and diglycosides of solasodine in BEC. Importantly, Cham does not disclose the existence of degradation products in BEC or the fact that they inhibit BEC activity. Rather, all Cham teaches one skilled in the art is that when BEC is administered in conjunction with rhamnose, its ability to prevent the death of

mice suffering from cancer is decreased i.e., the mode of action of BEC involves rhamnose.

Furthermore, in considering the disclosure in Cham, in its entirety it is important to note that the BEC preparations administered in the study were effective. For example, Cham (see Results and Discussion beginning on page 222), indicates that when four doses of BEC were given at 8mg per kg, all mice survived. This demonstration of efficacy of BEC in Cham teaches away from the present invention because it teaches one of ordinary skill in the art that there is no need to seek to refine BEC with a view to improving its efficacy. Thus, it further demonstrates that the problem associated with degradation products reducing potency of BEC was not perceived in the prior art. A person skilled in the art wishing to treat with BEC would simply follow this teaching. Thus, knowing the results can be achieved by following the prior art, there would be no motivation to seek to modify the prior art BEC compositions by cleaning or otherwise treating them to remove free rhamnose, as suggested by the Examiner. In other words, since the prior art BEC compositions were known to be effective, there was no problem in the art and certainly no teaching towards the refinement and modification of such compositions. It is only with the benefit of the knowledge of the present invention that the beneficial effects of cleaned BEC compositions can be appreciated.

The different nature/intention of the disclosure in Cham relative to the current invention is further reinforced by the fact that the amounts of rhamnose added to the BEC in Cham far exceeds the amount of free sugars removed by the methods of the present invention. Rhamnose at 5, 10 and 15mg per kg and/or weight were added

in the prior art methods whereas BEC at 8mg per kg of animal weight only has about 1.4mg per kg of rhamnose, being a degradation product of the glycoalkaloid in BEC. Again, the teachings in Cham do not render the present invention obvious because they in no way disclose or even suggest the problem addressed by the subject invention and thus do not in any way represent a motivation or suggestion to one of ordinary skill in the art to subject to BEC preparations to the method of present invention to improve their activity.

Moreover, the present invention provides unexpected and surprising results as described in the present Specification on page 7 which describes improved glycoalkaloid compositions and the surprising and unexpected discovery that glycoalkaloid formulations can be inhibited by free sugars resulting from degradation of the glycoalkaloid, all of which are not expected from the prior art. This provides secondary considerations of non-obviousness, which further reinforce that an important part of the present invention is the recognition of the problem associated with the degradation products. As indicated above, this problem is in no way taught or suggested by the disclosure in Cham.

In summary, at the time the present invention was made, it was not known that free sugars, resulting from the degradation of the glycoalkaloids in BEC, had any deleterious effect on the activity of BEC. Given that the problem was unknown there could not have been any motivation, as suggested by the Examiner, for a person of ordinary skill in the art to seek to apply the methods of the present invention to remove free sugars and thus improve the activity of the BEC compositions.

In view of the foregoing, Applicant respectfully submits that claims 24-63 are not obvious in view of Cham.

In view of the foregoing, Applicants respectfully submits that the application is in condition for allowance.

**END REMARKS**